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Original Article

Bardet Biedl Syndrome: A Rare Cause of Terminal Renal Disease

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Abstract: Bardet Biedl Syndrome is a rare ciliopathic type genetic disease, characterized by retinitis pigment, central obesity, polydactyly, and renal and genital system anomalies . Kidney failure, especially in advanced stages, is the most common cause of death. The diagnosis is based on clinical manifestations. The treatment is mainly symptomatic because each of the complications that appears should be treated during the course of the disease. **Key Words:** Bardet Biedl syndrome, ciliopathies, chronic renal disease, hemodialysis.

Introduction

Bardet Biedl Syndrome is a rare genetic disorder that has a prevalence of 1 in 140.000 to 1 in 160.000 newborns in North America and Europe[1]. The syndrome was first described by Georges Bardet and Arthur Biedl in 1920, and is an extremely rare disorder caused by mutations in up to 16 genes (BBS1 to BBS12, MKS1, NPHP6 / CEP290, SDCCAG8). It is transmitted by autosomal recessive inheritance, in which parents are heterozygotes and asymptomatic. Siblings have a 25% chance of being healthy, 50% will be heterozygous and 25% will be affected by the disease.

Three allelic inheritances involve the presence of at least three mutations to the manifested phenotype. However, it is currently unknown how much the multi alleles contribute to the phenotype[2,3]. Bardet Biedl syndrome is characterized by retinitis pigments, polydactyly, central obesity, kidney damage, intellectual disability and hypogonadism; and less frequently, by speech impairment, dental abnormalities, cardiovascular problems and *diabetes mellitus*[4]. Renal diseases may be structural or functional, and the most common is kidney failure, which occurs in 5-25% of cases. The clinical progression to chronic kidney disease reaches 4 -10% of patients, and this is the most common cause of death in patients with this syndrome[5,6]. The diagnosis can be concluded based on clinical features, and the treatment may include renal replacement therapy and renal transplantation[7, 8]

The disease is included in the group of ciliopathies, since it is resulting of at least 16 different genes mutations that are suspected of playing a key role in cilia, which are involved in cell movement and perception of sensory stimuli[2]. Ciliopathies are generally characterized by mutations in several genes associated to primary cilia, which are "finger-like" mobile or immobile cell structures. Mobile cilia generate fluid motion, and impairments in this structure are associated to infertility and bronchiectasis[3], whereas problems with immotile cilia are related to impairments of sensory perceptions.

Here we describe a rare case of this syndrome, which was diagnosed in the Nephrology department of Specialties Hospital "Eugenio Espejo" located in Quito, Pichincha

province, Ecuador, based in physical examination and clinical exams. The study was approved by the Committee on Bioethics in Research of the Specialist Hospital "Eugenio Espejo", and a consent signed by the legal representative (mother) of the patient was obtained.

Case Description

We report the case of a male patient, 21 years old. The patient was born in Pujilí (located 10 kilometers west from Latacunga, Cotopaxi Province, Ecuador) and he has been living in Quito for the lastest 8 years; without academic instruction, no occupation, and left-handed. The patient is the first gestation of a total of three siblings, from an unplanned pregnancy. Among prenatal findings, the mother reported a threatened abortion at 16 weeks gestation. He was born at home by vaginal natural childbirth, with weeping after near two minutes, in the 36th week of gestation. He was nursed until he was nine months old, and from that age on, he received supplementary feeding with incomplete immunization scheme and delayed psychomotor development evidenced in some milestones, like sitting alone at the age of one year and two months.

Also, he walked at the age of three and he did not build towers with blocks. From his birth, he presented polydactyly in his left hand (Fig. 1A) and lower limbs (Fig.1B).

Since his childhood, he presented morbid obesity until six months ago, in addition to hyperprolactinemia by not time specified; at age of 9 he is diagnosed with retinitis pigments, and at the age of 18 with 87% of bilateral blindness.

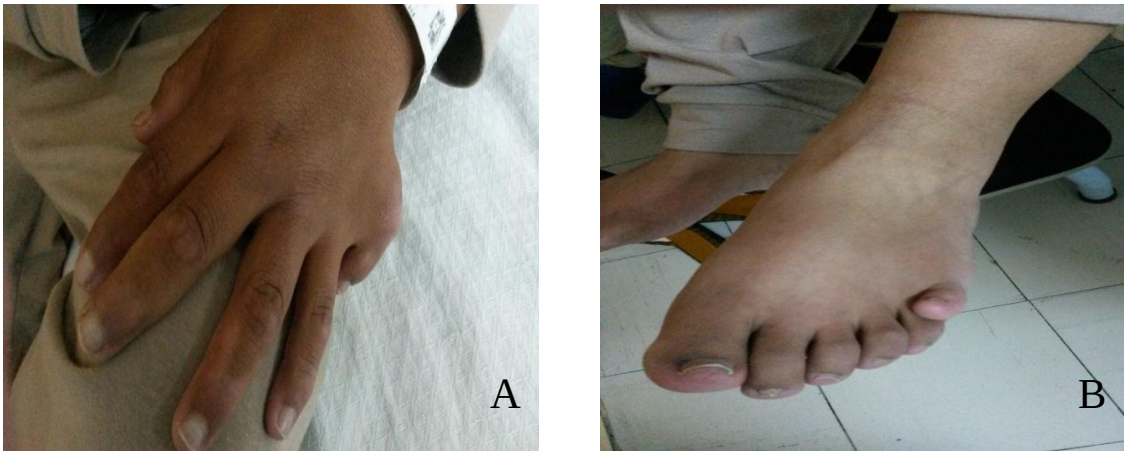

Figure 1: Polydactyly at (A) left hand, (B) right feet

No significant family background, alcoholic father up to the present. As habits, eating three times a day, three times a day voiding, defecation twice daily; consumption of alcohol, snuff and drug is not referred. In 2013, the patient was diagnosed with chronic kidney disease at Eugenio Espejo Hospital (Quito, Ecuador), requiring renal replacement therapy. However, his parents refused to start the treatment, so the patient remained without control of the disease. On the month of August (2015), he presented general malaise with hyporexia, weakness, nausea that did not reached vomiting, and oliguria. Thus, to the patient went to Enrique Garcés Hospital (Quito, Ecuador) where it was evidenced the criteria of emerging dialysis. He was referred to Eugenio Espejo Hospital for initiation of renal replacement therapy, where venous catheter jugular was placed in emergency and hemodialysis complication began.

The patient was oriented to proceed to physical examination. The physician in charge observed, an abnormal abdominal diameter was observed: (weight: 68.8 Kg, height: 1.48 cm, BMI: 31.41 Kg/m^2 weight), paleness, teeth in bad conditions, no palpable

lymphadenopathy in neck , chest with preserved expandability.

Cardiopulmonary system presented no abnormalities, and polydactyly was observed as shown in figures 1 and 2. Vital signs: blood pressure 153/104 mmHg, heart rate: 85 beats per minute, respiratory rate: 20 breaths per minute.

Laboratory tests revealed hemoglobin 9.20 g/dL (13.5 -17 g/dL), total white cells $5.93x10^3$/ul (5.00-10.00), differential count: 53% neutrophils (55-70%), 38% lymphocytes (20-40%), monocytes 6% (4-10%) and 0.8% eosinophils (1-4%), platelet count 320 x 10^3/µL (100-500x10^3/µL), total protein in serum 7.91 g/dL (6.6-8.7 g/dL), serum albumin 4.95 g /dL (3.5-5.2 g /dL); urea 199.5 mg /dL (6.6-48.5 mg /dL), creatinine 17.69 mg/dL (0.5- 0.9 mg/dL) (Modification of Diet in Renal Disease - MDRD: 3.64 mL/min 1.73m^2), sodium 145 mEq/L (135-145 mEq/L), potassium 4.76 mEq/L (3.5-5.5 mEq/L), calcium, 8.47 mg/dL (8.6-10 mg/dL), phosphorus 4.87 mg/dL (2.5-4.5 mg /dL), uric acid and 5.30 mg/dL (2,4-5.7 mg/dL).

Gas analysis values: pH 7.3 (7.35-7.45), pressure 27.4 carbon dioxide (34-45mmHg), bicarbonate 13.2 (18-24 mEq/L), excess base -11.4. Lipid profile: cholesterol 176 mg/dL (0-200 mg/dL), triglycerides 268 mg/dL (0-150 mg/dL), liver function was normal, Parathormone 703 (15-65 pg/mL), LH: 4.23 mIU/mL (1.7-8.6 mIU/mL), FSH 3.08 mIU/mL (0.7-11 mIU/mL), testosterone 414ηg/dL (300-1100 ηg/dL), 120.8 Prolactin. EMO (Urine Microscopic Elemental Examination) shows protein levels at 100 mg/dL. The exams to determine infection by Human Immunodeficiency Virus, Hepatitis B and C were all negative.

Normal kidneys with moderate increase of renal cortex echogenicity were identified by ultrasound, and reduction in the corticomedullar relationship (figure 2A), simple cyst in the right kidney was observed in the upper pole of 14 mm and a interpolate of 5 mm (figure 2b). A simple cyst of 10 mm diameter was observed in the upper pole of the left kidney.

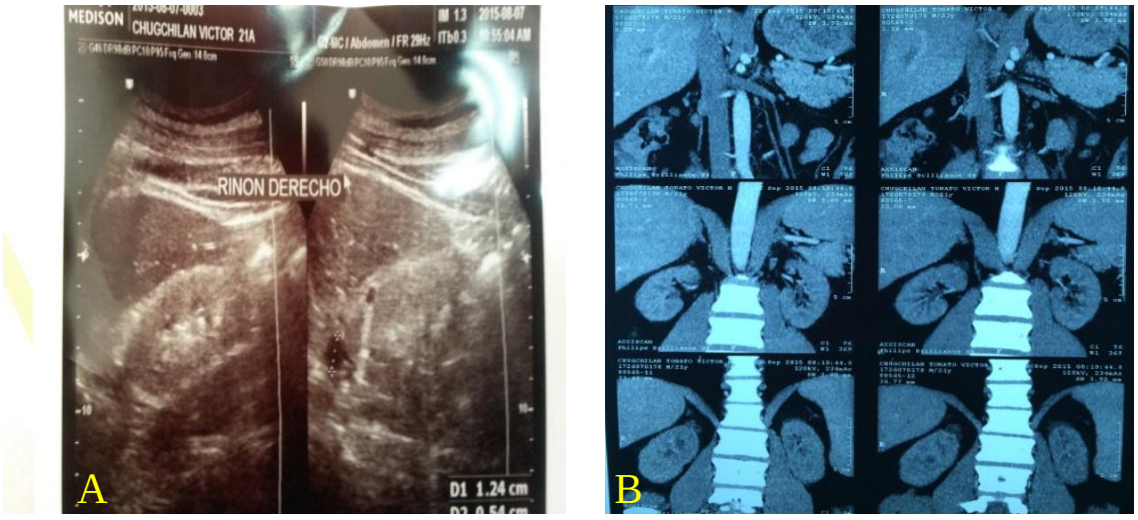

FIGURE 2: (A) Renal ultrasound: reduction in the corticomedullar relationship, (B) renal tomography: simple cysts

The patient was assessed by an ophthalmologist; a marked retinal atrophy was evident, along with vascular aging in both eyes (pigmentary retinitis). The patient was also assessed by a psychologist. The IQ assessment was performed, and the coefficient 53 was obtained; this is suggestive of mild mental disability. Endocrinology examination indicated Tanner IV (testicular volume between 12 and 20 ml. The scrotum enlarges and darkens more. The penis increases in length to 10 cm, and there is no difference to the glans in age ranging from 12.5 and 14 years, with testicular volume of 25 cm^3. With all these clinical and laboratory findings, Chronic Kidney Disease, terminal stage was diagnosed. He remained hospitalized for nine days and hemodialysis was performed without complications evolving favorably. The patient remains receiving therapy three times a week and protocol studies of renal transplantation began in this institution.

Discussion

The syndrome is included within the broad category of ciliopathies, produced by primary ciliary dysfunction, showing alterations in nerve signaling pathways and impaired perception of sensory stimuli. Clinical features include early onset dystrophy in the retina, obesity, limb defects and kidney abnormalities as major criteria; and less common mental disability, hypogonadism, *diabetes mellitus*, anosmia, cardiac abnormalities, dental abnormalities, slurred speech. According to these data, at least four major and two minor criteria together are enough to diagnose the Bardet Biedl Syndrome[9].

The most frequent finding is the retinal dystrophy in the form of retinitis pigmentosa, which in most cases the total loss of vision, is developed before the second decade[2, 10]. Central obesity is the second most common clinical finding; the incidence ranges from 72 to 92%. Generally, the weight at the moment of birth is normal. Obesity begins in early childhood and increases over time in patients who suffer from this syndrome. Limb abnormalities as polydactyly and syndactyly are followed from birth and are telltale signs for early diagnosis. Usually postaxial polydactyly is evident in both hands and feet[10].

Renal anomalies, as part of this syndrome have recently been recognized; renal parenchymal cysts, fetal lobation and scars, dysplastic kidney, unilateral agenesis, vesicoureteral reflux, bladder obstruction, horseshoe kidney, ectopic kidney. It should be mentioned that in most studies, chronic renal failure has a very low incidence rate of about 5%, the most common cause of death in these patients. All three modes of renal replacement therapy: hemodialysis, peritoneal dialysis and transplantation can be used optimally in these patients[3,7].

Mental disability is the fourth most important feature of the syndrome. Psychosocial development is delayed and the results of IQ tests are low. Cognitive dysfunction is seen in most cases after starting school. It has been shown that primary cilia is one of the most important organelles in the human brain and are necessary for the development stages of the hippocampus[5,9].

Hypogonadism as another important criterion, it may be delay in the onset of puberty in both sexes; It is more common in men, while genital abnormalities such as hypoplasia of the fallopian tubes, vaginal atresia, hematocolpos and vesico-vaginal fistulas are more common in women. The small size of the penis and the decrease in testicular volume is common, there is often a delay in the onset of the menstrual cycle[1,2,9].

A young adult patient who met the clinical criteria of Bardet Biedl entered to the Nephrology emerging with dialytic criteria (significant azotemia, metabolic acidosis, signs of fluid overload). It is cataloged as a Terminal Chronic renal Disease (MDRD <15 $mL/min/m^2$) and it starts renal replacement therapy.

As discussed, renal anomalies are part of this syndrome and have been reported recently. The frequency of these anomalies is rare, although they are the main cause of death in these patients. Regarding the treatment, this

syndrome does not contraindicate the application of any of the three modes, as in the case of this patient, which currently has passed three-week hemodialysis (by the moment of submission of this paper); and may be a candidate for kidney transplant, although some studies[11,12] have reported that the post-intervention patients have risk of severe obesity, cancers and cardiovascular complications.

Conclusion

The diagnosis for a patient with Bardet Biedl syndrome is based on the fulfillment of major and minor clinical criteria, without the use of laboratory resources, as it is documented in some studies of other case reports. The syndrome is a rare cause of chronic kidney disease. The complete elucidation of the genetics and pathophysiology can be used to investigate therapeutic options in the future.

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